Intradialytic Hypertension

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Agenda

- Introduction
- Definition and Prevalence
- Clinical Characteristics
- Outcome and Prognosis of IDH
- Pathophysiologic Mechanisms
- Treatment
- Conclusions

Introduction

- Many nephrologists have been paged during calls by dialysis nurses because one of their patients was presenting with severe hypertension at the time of dialysis disconnection.

- IDH occurs in *5% to 15%* of treatments and it is a risk factor for cardiovascular morbidity and mortality.

- It has been called *paradoxical hypertension* because it occurs during ultrafiltration and with Na clearance. IDH often happens in patients starting the dialysis treatment *"incident patients"* but is also seen in patients treated for months or years with dialysis *"prevalent patients"*.

Definition

- There is **no** uniform definition of IDH. It is not necessary to frame this definition with strict numbers.
- It can be defined as a sustained increase of blood pressure during the dialysis session with BP values during and at the end of the dialysis session exceeding BP values at dialysis onset.
- It may also happen when the predialysis BP is high and then becomes even higher during the usual hourly BP check and at the dialysis disconnection.
- Increase in BP that is resistant to ultrafiltration. This BP rise may be very severe with an impressive hypertension crisis.
- The repetition of the phenomenon over the sessions must alert the physician and trigger clinical decision.

Definition

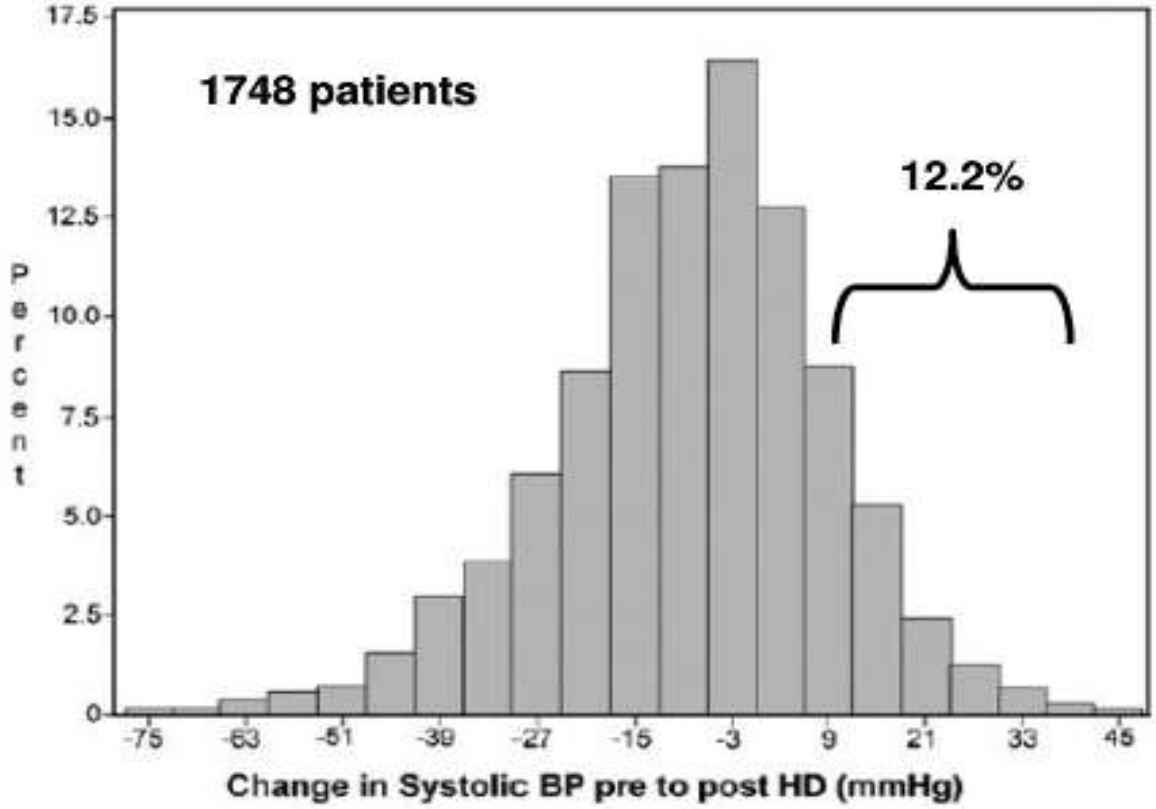
Definitions of IDH from clinical studies and reviews

Reference	Definitions of IDH
Amerling et al.	
Cirit et al.	
Gunal et al.	
Chou et al.	
Chen et al	
Inrig et al.	

Chazot , Nephron Clin Pract 2010

Prevalence

Dialysis Morbidity Mortality Wave 2 cohort



Inrig AJKD 2007

Clinical Characteristics

Patients with intradialytic HTN:

- Older age
- Lower body mass index
- Lower interdialytic weight gain
- Lower serum albumin, serum creatinine and serum phosphorus levels
- More pre - dialysis HTN.
- Tend to be on more anti HTN medications.

Inrig et al Am J Kidney Dis 2009

Prognostic

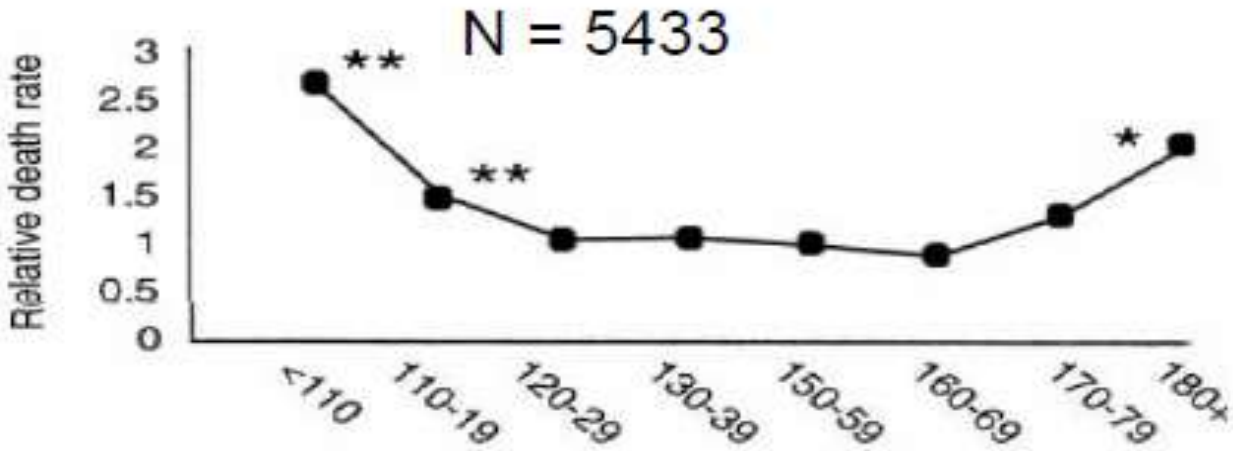
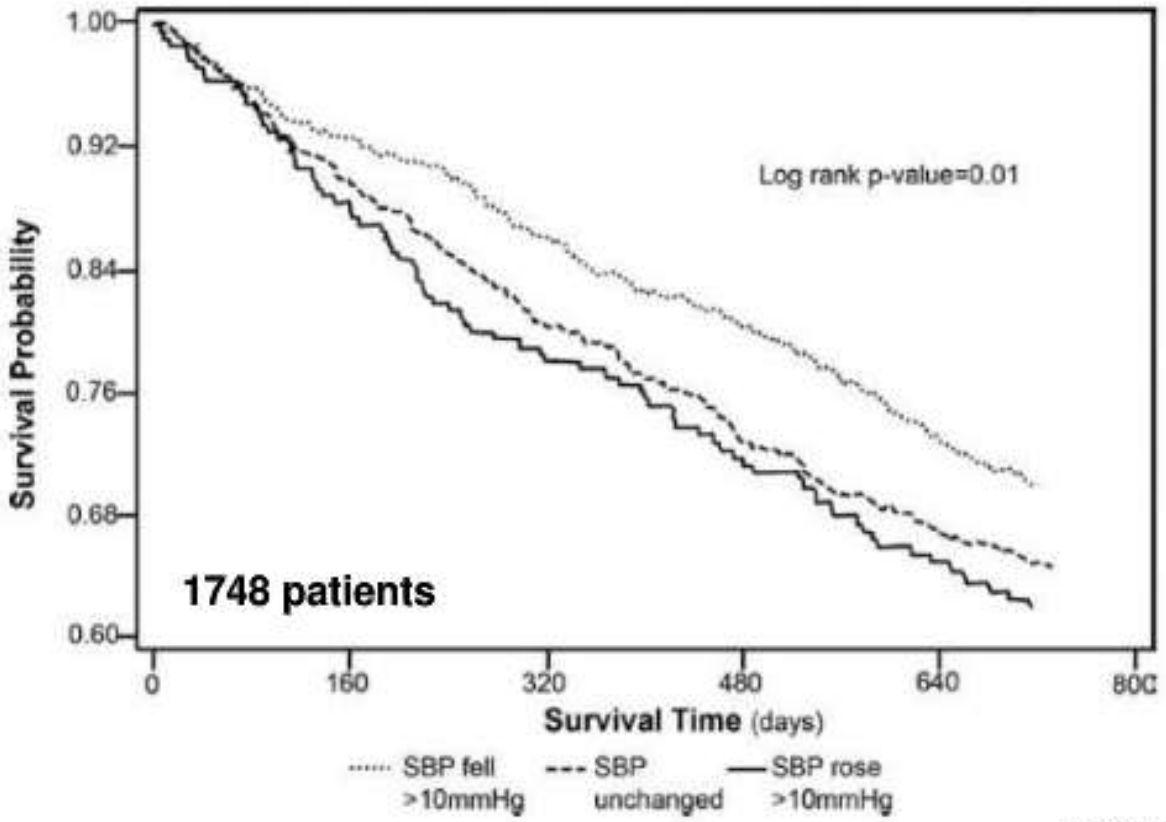


Fig. 1. Systolic blood pressure post-dialysis (SBP; time-varying) and cardio/cerebrovascular mortality in hemodialysis (HD) patients 1992 to 1996. The "U" curve relationship between SBP post-dialysis and mortality is: SBP $<$ 110 mm Hg, RR = 2.62, $^{**}P < 0.01$ versus reference 140 to 49; SBP 110 to 19 mm Hg, RR = 1.48, $^{**}P < 0.01$ versus reference; SBP $\geq$ 180 mm Hg, RR = 1.06, $^{*}P < 0.05$ versus reference.

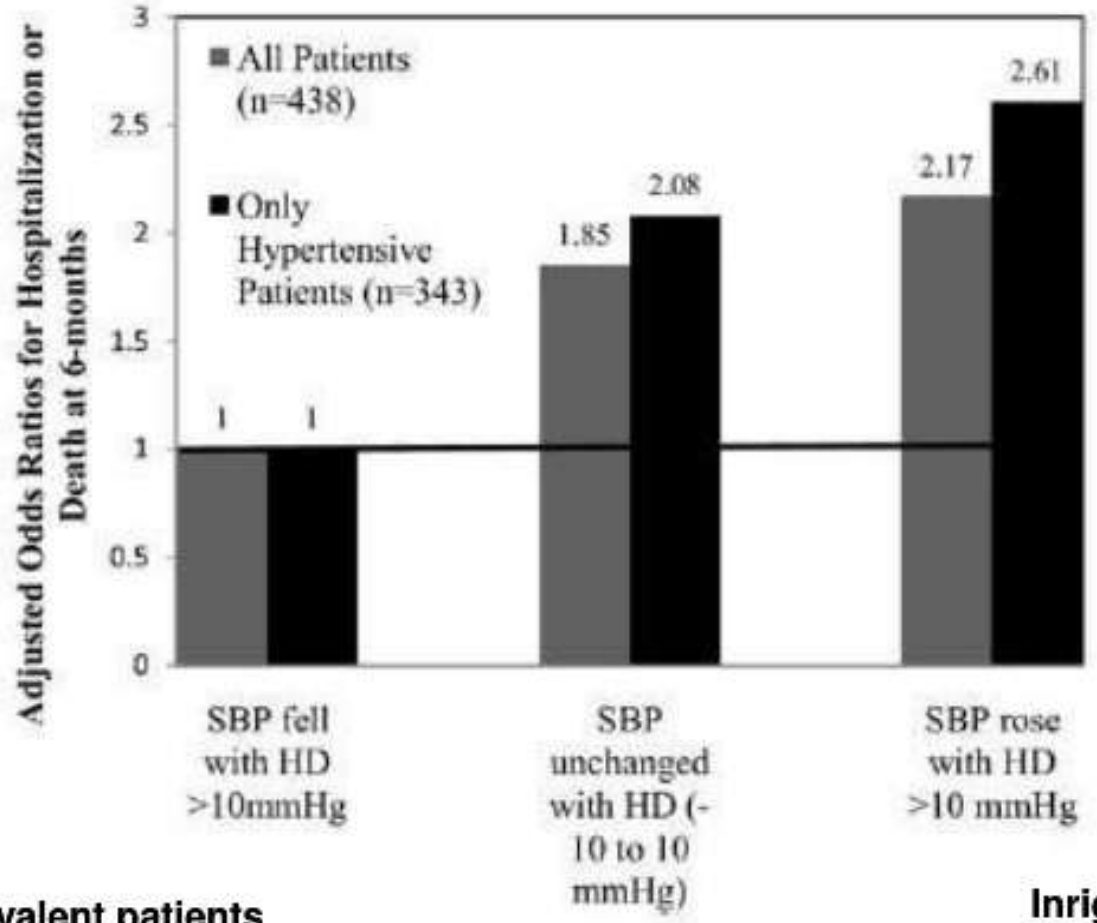
Zager et al Kidney Int 1998

Intradialytic hypertension and outcomes

Dialysis Morbidity Mortality Wave 2 cohort



Inrig AJKD 2007



438 prevalent patients

Inrig AJKD 2010

Postdialysis blood pressure rise predicts long-term outcomes in chronic hemodialysis patients: a four-year prospective observational cohort study

Background

The blood pressure (BP) of a proportion of chronic hemodialysis (HD) patients rises after HD. We investigated the influence of postdialysis BP rise on long-term outcomes.

Methods

A total of **115** prevalent HD patients were enrolled. Because of the fluctuating nature of predialysis and postdialysis BP, systolic BP (SBP) and diastolic BP (DBP) before and after HD were recorded from **25** consecutive HD sessions during a **2**-month period. Patients were followed for **4** years or until death or withdrawal.

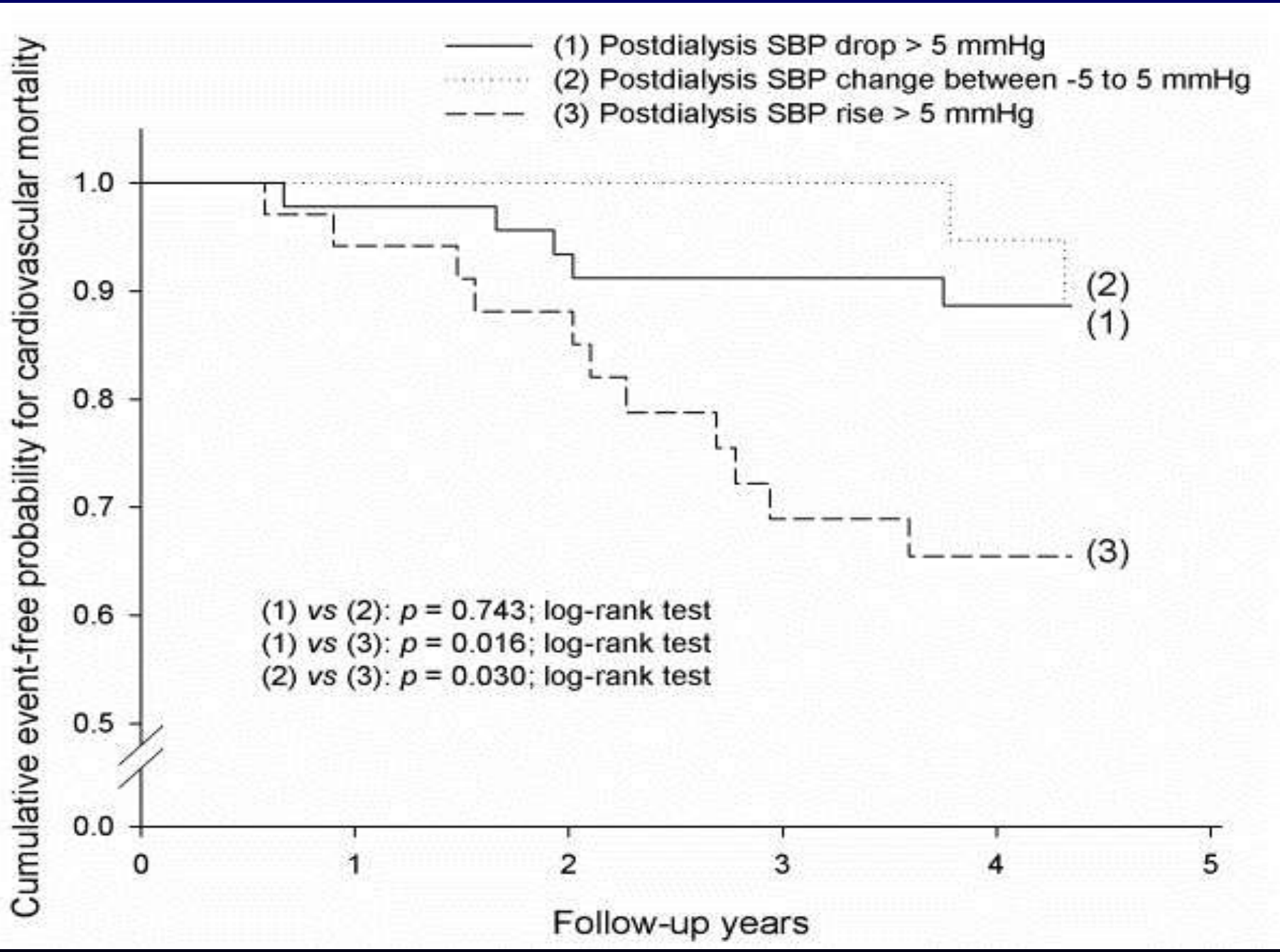
Results

Kaplan-Meier estimates revealed that patients with average postdialysis SBP **rise of > 5** mmHg were at the highest risk of both cardiovascular and all-cause mortality as compared to those with an average postdialysis SBP change between **-5 to 5** mmHg and those with an average postdialysis SBP **drop of > 5** mmHg.

Furthermore, multivariate Cox regression analysis indicated that both postdialysis SBP **rise of > 5** mmHg (HR, 3.925 [95% CI, 1.410-10.846], $p = 0.008$) and high cardiothoracic (CT) ratio of more than 50% (HR, 7.560 [95% CI, 2.048-27.912], $p = 0.002$) independently predicted all-cause mortality. We also found that patients with an average postdialysis SBP rise were associated with subclinical volume overload, as evidenced by the significantly higher CT ratio ($p = 0.008$).

Conclusions

A postdialysis SBP rise in HD patients independently predicted 4-year cardiovascular and all-cause mortality. Considering postdialysis SBP rise was associated with higher CT ratio, intensive evaluation of cardiac and volume status should be performed in patients with postdialysis SBP rise.


(1) Postdialysis SBP drop > 5 mmHg
(2) Postdialysis SBP change between -5 to 5 mmHg
(3) Postdialysis SBP rise > 5 mmHg
Cumulative event-free probability for cardiovascular mortality
1.0
0.9
0.8
0.7
0.6
0.5
0.0
0
1
2
3
4
5
Follow-up years
(2)
(1)
(3)
(1) vs (2): p = 0.743; log-rank test
(1) vs (3): p = 0.016; log-rank test
(2) vs (3): p = 0.030; log-rank test

Pathophysiologic Mechanisms

Box 1. Potential Pathophysiologic Mechanisms of Intradialytic Hypertension

- Volume overload
- Sympathetic overactivity
- Activation of the renin-angiotensin-aldosterone system
- Endothelial cell dysfunction
- Dialysis-specific factors
  - Net sodium gain
  - High ionized calcium
  - Hypokalemia
- Medications
  - Erythropoietin-stimulating agents
  - Removal of antihypertensive medications
- Vascular stiffness

Inrig, Am J Kidney Dis 2009

Volume overload

« When the BP increase during the session, decrease the weight »

Tassin aphorism

Sympathetic overactivity

- Sympathetic overactivity is correlating with the increase in both vascular resistance and systemic BP .
- The mechanism by which this occurs is unclear, but the afferent signal may arise within the kidney, since sympathetic activation is not seen in anephric patients .
- Activation of chemoreceptors within the kidney by uremic metabolites may play an important role. Its activation leads to a neural reflex that traverses afferent pathways to the central nervous system, resulting in increased efferent sympathetic tone.
- A study that measured plasma catecholamines in patients with and without intradialytic hypertension pre and post dialysis found that norepinephrine were actually higher in controls post dialysis.

Kidney International (2006) 69, 1833–1838

Activation of Renin Angiotensin Aldosterone System

- Volume removal followed by upregulation of homeostatic systems with consequent activation of RAAS is often cited as a possible cause of intradialytic hypertension.
- However, a study that measured plasma renin in patients with and without intradialytic hypertension pre and post dialysis found that renin was actually higher in controls post dialysis.

Kidney International (2006) 69, 1833–1838

Physiological changes during hemodialysis in patients with intradialysis hypertension

Laboratory data before and after hemodialysis

	Hypertension prone	Controls	*P*-value
Before hemodialysis			
Plasma potassium (mEq/l)	4.4 ± 0.3	4.4 ± 0.5	NS
Plasma free calcium (mg/dl)	4.2 ± 0.1	4.4 ± 0.1	NS
Plasma epinephrine (pg/ml)	97.1 ± 13.5	99.0 ± 8.5	NS
Plasma norepinephrine (pg/ml)	225 ± 43	253 ± 47	NS
Plasma renin concentration (pg/ml)	10.8 ± 3.4	15..1 ± 3.1	NS
After hemodialysis			
Plasma potassium (mEq/l)	3.2 ± 0.1*	3.3 ± 0.1*	NS
Plasma free calcium (mg/dl)	5.0 ± 0.1*	5.1 ± 0.1*	NS
Plasma epinephrine (pg/ml)	87.6 ± 9.8	100.4 ± 6.8	NS
Plasma norepinephrine (pg/ml)	204 ± 27	363 ± 62*	<0.05
Plasma renin concentration (pg/ml)	10.6 ± 2.8	24.9 ± 7.3*	<0.05

Kidney International (2006) 69, 1833–1838

Endothelial cell dysfunction

- An intriguing concept regarding the pathogenesis of IDH is abnormal endothelial release of hemodynamically active compounds and elevated plasma levels of the potent VC endothelin-1 have been found in uremic subjects.
- The development of a method to inhibit the activity of endothelin (such as a receptor blocker) will be necessary to determine the physiologic importance of endothelin in these patients.
- There is evidence that uremic plasma contains a higher level of an endogenous compound ADMA (asymmetrical dimethylarginine) that is an inhibitor of nitric oxide “VD” synthesis. This observation raises the possibility that nitric oxide deficiency may contribute to the development of IDH.

Endothelial Cell Dysfunction

Plasma concentrations of nitric oxide (nitrate+nitrite) and endothelin (ET-1) before and after hemodialysis

	Hypertension prone	Control	*P*-value
Before hemodialysis			
NO (μM)	41.2±6.1	32.9±4.5	NS
ET-1 (pg/ml)	345.6±34.5	287.4±29.3	NS
NO/ET-1	0.869±0.502	0.129±0.013	NS
After hemodialysis			
NO (μM)	7.2±0.9**	7.9±0.9**	NS
ET-1 (pg/ml)	510.9±43.3**	276.7±30.1	<0.05
NO/ET-1	0.018±0.003**	0.034±0.005**	<0.05

Abbreviations: NO, nitric oxide; ET-1, endothelin; NS, not significant.
All data are presented as mean±s.e.m.
*$P<0.05$ when compared with values before hemodialysis, **$P<0.005$ when compared with values before hemodialysis.

Chou, et al Kidney Int 2006

Intradialytic hypertension and its association with endothelial cell dysfunction.

Inrig JK, Van Buren P, Kim C, Vongpatanasin W, Povsic TJ, Toto RD

Clin J Am Soc Nephrol. 2011 Aug; 6(8):2016-24. Epub 2011 Jul 14.

BACKGROUND AND OBJECTIVES: Intradialytic hypertension is associated with adverse outcomes, yet the mechanism is uncertain. Patients with intradialytic hypertension exhibit imbalances in endothelial-derived vasoregulators nitric oxide and endothelin-1, indirectly suggesting endothelial cell dysfunction. We hypothesized that intradialytic hypertension is associated in vivo with endothelial cell dysfunction, a novel predictor of adverse cardiovascular outcomes.

DESIGN, SETTINGS, PARTICIPANTS,MEASUREMENTS: We performed a case-control cohort study including 25 hemodialysis (HD) subjects without (controls) and 25 with intradialytic hypertension (an increase in systolic BP pre- to postdialysis≥10 mmHg≥4/6 consecutive HD sessions). The primary outcome was peripheral blood endothelial progenitor cells (EPCs) assessed by aldehyde dehydrogenase activity (ALDH (br)) and cell surface marker expression (CD34 (+) CD133 (+)). We also assessed endothelial function by ultrasonographic measurement of brachial artery flow-mediated vasodilation (FMD) normalized for shear stress. Parametric and nonparametric t tests were used to compare EPCs, FMD, and BP.

RESULTS: Baseline characteristics and comorbidities were similar between groups. Compared with controls, 2-week average predialysis systolic BP was lower among subjects with intradialytic hypertension (144.0 versus 155.5 mmHg), but postdialysis systolic BP was significantly higher (159.0 versus 128.1 mmHg). Endothelial cell function was impaired among subjects with intradialytic hypertension as measured by decreased median ALDH(br) cells and decreased CD34(+)CD133(+) cells (ALDH(br), 0.034% versus 0.053%; CD34(+)CD133(+), 0.033% versus 0.059%). FMD was lower among subjects with intradialytic hypertension (1.03% versus 1.67%).

CONCLUSIONS: Intradialytic hypertension is associated with endothelial cell dysfunction. We propose that endothelial cell dysfunction may partially explain the higher event rates observed in these patients.

Net Sodium gain

- Intradialytic sodium gain due to higher dialysate than plasma sodium has been suggested as a possible cause of intradialytic hypertension but has not been directly studied. Sodium appears as the culprit for IDH.

- In HD patients, the sodium balance becomes positive when dietary sodium intake exceeds sodium removal during dialysis and a low sodium diet should be advised in most dialysis patients .

- **Oberleithner et al;** demonstrated a dramatic and rapid stiffening effect of cultured endothelial cells in a high sodium concentration medium that was associated with NO synthesis down-regulation.

High ionized Calcium and Hypokalemia

- Dialysis induced reductions in serum potassium “direct VC effect” and elevations in calcium “increase myocardial contractility and cardiac output” have also been postulated as possible causes but in the same study no statistical significant difference between groups in these electrolytes was found.

Chou et al Kidney Int 2006

Potassium – Calcium

- Hypokaliemia: direct vasoconstrictor effect
- Acute increase Ca^{++}: increases myocardial contractility and cardiac output

Summary of pre/post variations of biochemical/endocrine markers in IDH patients and in controls in the study by Chou et al.

Pre/Post (plasma)	IDH group	Control group	p value between groups
K^+	↓	↓	NS
Ca^{2+}	↑	↑	NS

Chou et al Kidney int 2006

Summary of pre/post variations of biochemical/endocrine markers in IDH patients and in controls in the study by Chou et al.

Pre/Post (plasma)	IDH group	Control group	p value between groups
Epinephrine	↔	↔	NS
Norepinephrine	↔	↑	<0.05
Renin	↔	↑	<0.05
Endothelin	↑	↔	<0.05
K^+	↓	↓	NS
Ca^{2+}	↑	↑	NS

Erythropoietin- Stimulating Agents

- An increase in BP of 10 mmHg or more may occur in patients with renal failure who are treated with erythropoietin. The risk is greatest in those with rapid correction of severe anemia and with preexistent hypertension.

- IV administration of rHuEPO has been associated with elevations in blood pressure in dialysis patients and interestingly also with elevations in endothelin-1.

- Changing the administration of rHuEPO from the IV to the SC route has been associated with improved blood pressure control in hypertensive dialysis patients.

Removal of Antihypertensive Medications

- Many blood pressure medications including beta-blockers and ACE inhibitors are significantly removed during dialysis.
- The removal of these agents is a potential contributor in many cases.

Antihypertensive medications

TABLE 2. Pharmacokinetics of select antihypertensive agents in hemodialysis (15,68,69)

Class	$T^{1/2}$ in ESRD	Range of dosing (initial to usual or maximum)	% Removal with hemodialysis
Angiotensin converting enzyme inhibitors			
Captopril	20–30 hours	12.5–50 mg q24 hours	Yes
Benazepril	?	5–40 mg q24 hours	20–50%
Enalapril	Prolonged	2.5–10 mg q24 to 48 hours	35%
Fosinopril	Prolonged	10–80 mg q24 hours	<10%
Lisinopril	54 hours	2.5–10 mg q24–48 hours	50%
Ramipril	prolonged	2.5–10 mg q24 hours	<30%
Angiotensin receptor blockers			
Losartan	4 hours	50–100 mg q24	None
Candesartan	5–9 hours	4–32 mg q24	None
Eprosartan	?	400–600 mg q24	None
Telmisartan	24 hours	40–80 mg q24	None
Valsartan	6 hours	80–160 mg q24	None
Irbesartan	11–15 hours	75–300 mg q24	None
Aldosterone antagonists			
Spironolactone[a]	?	25–50 mg qd	None
Eplerenone[b]	?	50–100 mg qd	None
Renin inhibitor			
Aliskiren	?	150–300 mg qd	?

Inrig, Semin Dialysis 2010

Potential strategies for the treatment of intradialytic hypertension

Potential strategies for the treatment of intradialytic hypertension	
Potential strategy	**Potential methods**
Reduce volume overload	
Control electrolyte changes	
Reduce sympathetic overactivity	
Inhibit the renin–angiotensin–aldosterone system	
Evaluate concurrent therapies	

Locatelli et al Nat. Rev. Nephrol. 2009

Treatment

- The first-line treatment of IDH is fluid removal. The amount of removed fluid was equivalent to 7.5–11% of the body weight in days or weeks.

- However, it must be done with caution to avoid hazardous BP drops that may occur in elderly or patients with severe comorbidity.

- Longer or more frequent dialysis may be necessary to avoid the UF side effects or hasten the amelioration of this complication.

Treatment

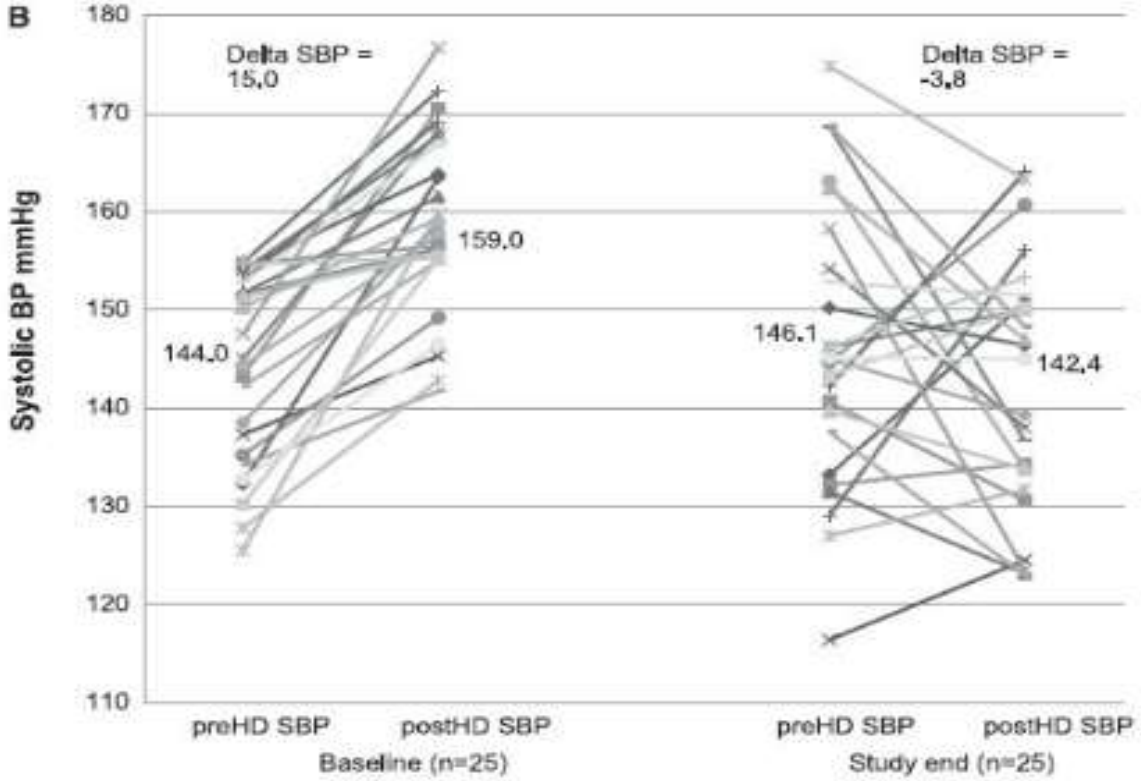
- Achieving adequate sodium solute removal during hemodialysis.
- Limiting the use of high-calcium dialysate.
- Avoidance of dialyzable antihypertensive medications.
- Inhibit the renin-angiotensin- aldosterone system.
- Use medication that decrease arterial stiffness.
- Reducing erythropoeitin dose in patients with severe hypertension.
- Nephrectomy in resistant cases.
- Renal transplantation or conversion to PD.

Treatment

- Carvedilol, which blocks endothelin-1 release, appears to be effective in this setting.
- This was suggested by a 12-week pilot study in which the initiation of carvedilol titrated to 50 mg twice daily was associated with a decrease in the frequency of intradialytic hypertensive episodes from 28 to 77 % of hemodialysis sessions.

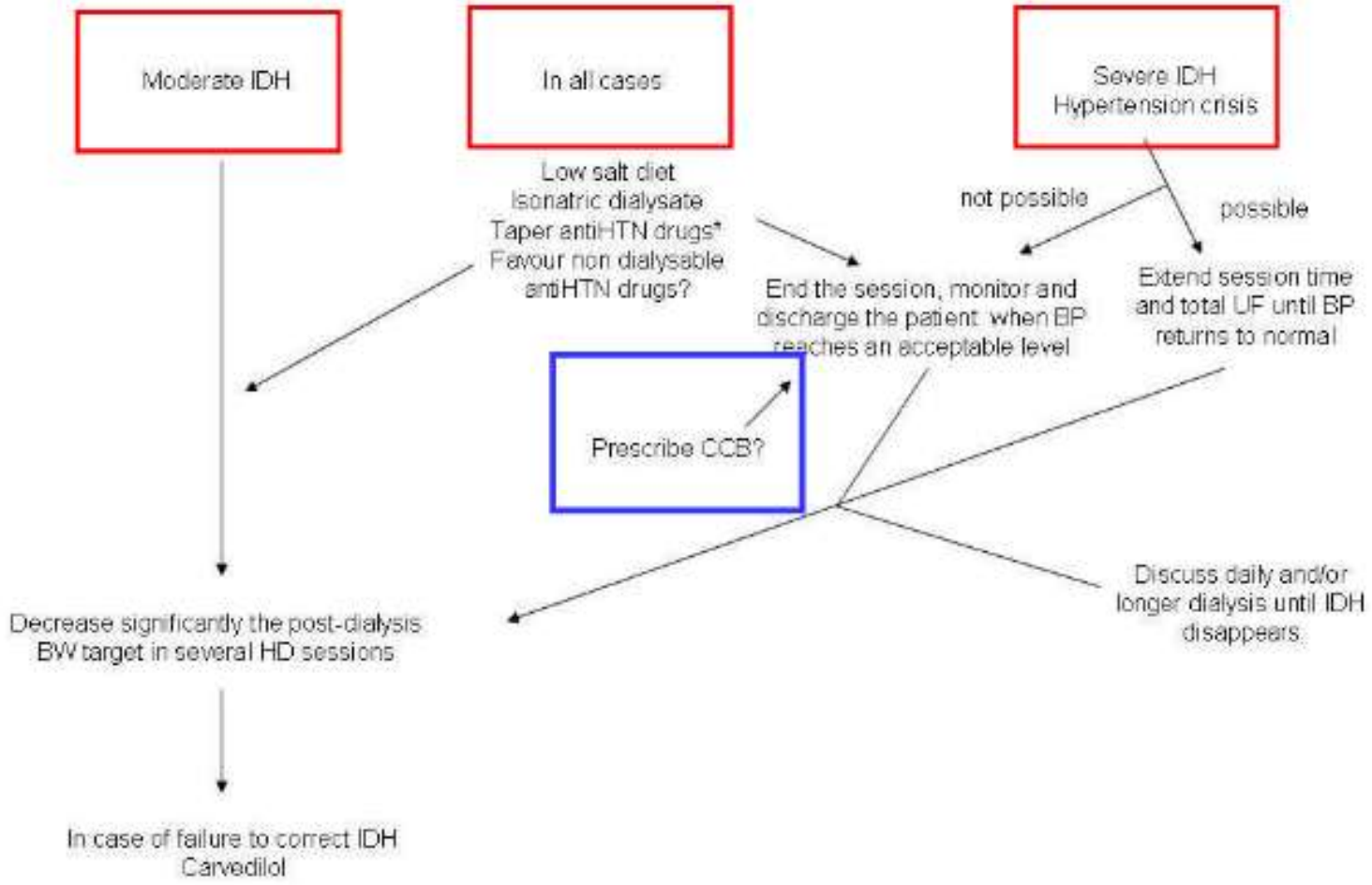
Inrig et al, CJASN 2012

Use of Carvedilol to treat intradialytic hypertension 50mg twice daily



Improvement of flow-mediated vasodilation

Inrig cJASN 2012



* In cases of UF-induced hypotension episodes
CCB: Calcium Channel Blockers; antiHTN: antihypertensive; BP: blood pressure; UF: ultrafiltration

Chazot, Nephron Clin Pract 2010 modified

Conclusions

- IDH present in 5-15% of HD patients that is commonly ignored.
- IDH is an unusual expression of extracellular fluid overload. It is efficiently corrected by fluid removal with careful attention to the optimal dry body weight.
- Important role of endothelial cell dysfunction.
- Select antihypertensive medications according to the elimination profile and the use of receptor blockers.
- In IDH crisis prolong the HD session and daily dialysis if possible.
- Improving our knowledge of this complication will contribute to decreasing the high burden of cardiovascular morbidities and mortality occurring in dialysis patients.

THANK YOU